PREVALENCE OF NONMOTOR FEATURES ACROSS THE VARIOUS STAGES OF IDIOPATHIC PARKINSON'S DISEASE AND ITS CORRELATION WITH THE SEVERITY AND DURATION OF THE DISEASE

Submitted in partial fulfillment of the requirements towards the conferment of

BRANCH - I D.M. NEUROLOGY

of

THE TAMILNADU

DR.M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMILNADU

AUGUST 2010

INSTITUTE OF NEUROLOGY

MADRAS MEDICAL COLLEGE

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CERTIFICATE

This is to certify that this dissertation entitled **"PREVALENCE OF NONMOTOR FEATURES ACROSS THE VARIOUS STAGES OF IDIOPATHIC PARKINSON'S DISEASE AND ITS CORRELATION WITH THE SEVERITY AND DURATION OF THE DISEASE"** submitted by **Dr.N.Shobana** appearing for **D.M.,** Degree examination in **August 2010** is a bonafide record of work done by her under my direct guidance and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

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DECLARATION

I **Dr. N. Shobana** do solemnly affirm that this dissertation titled **"PREVALENCE OF NONMOTOR FEATURES ACROSS THE VARIOUS STAGES OF IDIOPATHIC PARKINSON'S DISEASE AND ITS CORRELATION WITH THE SEVERITY AND DURATION OF THE DISEASE"** is done by me at Institute of Neurology, Madras Medical College & Govt. General Hospital, Chennai, during 2008-2010 under the guidance and supervision of **Prof.R.M.Boopathy M.D., D.M., Professor of Neurology, Institute of Neurology.**

The dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of **D.M., Degree in Neurology.**

Place: Chennai

Date: 25.05.2010

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SPECIAL ACKNOWLEDGEMENT

I gratefully acknowledge and sincerely thank **Dr. J. Mohanasundaram M.D. Ph.D., DNB Dean Madras Medical College,** Chennai for permitting me to do this Dissertation and utilize the Institutional facilities.

ACKNOWLEDGEMENT

My sincere thanks to **Prof. V. Sundar,** Professor and Head, Institute of Neurology for his immense kindness in allowing me to use the services of the department.

I thank **Prof.R.M.Boopathy,** Professor of Neurology, Institute of Neurology, with profound gratitude for his constant guidance, motivation, advice and valuable criticism, kindness and encouragement which enabled me to complete this work.

I thank **Prof. A.V.Srinivasan, Pro.V.Natarajan,** former Professors, **Prof. C. Mutharasu, Prof. K.Bhanu, Prof. Gopinathan,** Professors, Institute of Neurology for their constant guidance and encouragement.

I thank with gratitude, **Dr. V. Kamaraj, Dr.S.Arunan, Dr. M. Jawahar** and **Dr.P.Muthukumar** for their constant encouragement.

I thank my postgraduate friends for their constant support, all the technical & non technical staffs of the Institute of Neurology, for their cooperation.

Last but the most, I thank each of my patients for cooperating for the study in spite of their pain and suffering.

CONTENTS

INTRODUCTION

Non motor symptoms(NMS) in Parkinson's Disease constitutes a major clinical challenge, as they are common, yet often overshadowed by the dominance of motor symptoms and high awareness of these among treating health care professionals. The NMS of PD were recognised by James Parkinson himself. Thus in his essay on the shaking Palsy in 1817, he referred to sleep disturbances, dysathria, constipation, dysphagia, sialorhoea, urinary incontinence, constant sleepiness with slight delirium. Since then numerous studies have indicated that NMS are frequent accompaniments of PD affecting memory, bladder and bowel and sleep among others. These NMS significantly affect the quality of life and may precipitate hospitalization. Although common the NMS of PD are not well recognised in clinical practice. While some such as depression, dementia, autonomic and sleep disturbances are well known, others such as dysphagia, dribbling of saliva, weight changes, sexual problems and diplopia are less well recognised.

The NMS include neuropsychiatric symptoms, sleep disorders, autonomic symptoms, sensory symptoms and miscellaneous symptoms like diplopia, fatigue and seborhea. The nonmotor symptoms questionnaire (NMS Quest) and the nonmotor symprom scale (NMSS) were developed to assess the frequency and severity of NMS in PD patients across all stages. The NMS Quest was validated in march 2007

by the Movement Disorder Society. It covers 9 domains and includes 30 items, including sleep / fatigue, cardiovascular, mood/cognition, perceptual problems, attention / memory, gastrointestinal, urinary, sexual functions and miscellaneous. The NMS Quest does not provide an overall score or disability and is not a graded rating instrument. It is a screening tool designed to draw attention to the presence of NMS and to initiate further investigation.

Recent studies using the NMS Quest for PD patients have highlighted the significant occurrence of a range of different NMS in PD patients. Further studies validating the nonmotor symptom scale (NMSS) also indicated a strong relationship between the burden of NMS in PD and health related quality of life (QOL).The development of tools such as the NMS Quest and NMSS alongside the revamped UPDRS which includes a specific nonmotor domain will help define research and therapy to improve the recognition and managememt of NMS of PD.

AIMS AND OBJECTIVES

1. To study the prevalence of nonmotor features across the various stages of Idiopathic Parkinson's Disease and

2. To correlate it with the severity and duration of the disease.

MATERIALS AND METHODS

Patients with Idiopathic Parkinson's Disease who attend the Movement Disorder clinic at the Institute of Neurology were studied. A detailed and complete neurological examination was done. Imaging, CT and MRI brain was done to exclude Parkinson Plus syndromes and vascular parkinsonism. The patients were in the age group of more than 50 years and the disease duration varied between less than 5 years,5 to 10 years and more than 10 years. The motor symptoms were assessed through the Unified Parkinson's Disease Rating Scale(UPDRS) and the disease staged according to the Hoehn and Yahr staging from stage 0 to stage 5.The nonmotor features were assessed through the Nonmotor Symptoms Questionnaire(NMS QUEST) which contains 30 items. This included cognitive dysfunction,sleep disorders,autonomic abnormalities, fatigue and depression. The prevalence of these Nonmotor symptoms across the various stages of the disease was studied and its correlation with the disease severity and duration assessed.

INCUSION CRITERIA:

1 Idiopathic Parkinson's Disease patients with the age of onset of the disease at 50 years and above

EXCLUSION CRITERIA:

1. Young onset Parkinson's Disease(YOPD) with the age of onset below 50 years

2. Parkinson's Plus Syndromes like Progressive Supranuclear Palsy(PSP), Multi System Atropy (MSA), Corticobasal Degeneration(CBD)

3. Patients with Vascular Parkinsonism.

REVIEW OF LITERATURE

Parkinson’s Disease (also known as **Parkinson disease** or **PD**) is a degenerative disorder of the central nervous system that often impairs the sufferer's motor skills, speech, and other functions. It is characterized by muscle rigidity, tremor, a slowing of physical movement (bradykinesia) and a loss of physical movement (akinesia) in extreme cases. The primary symptoms are the results of decreased stimulation of the motor cortex by the basal ganglia, normally caused by the insufficient formation and action of dopamine, which is produced in the dopaminergic neurons of the brain. Secondary symptoms may include high level cognitive dysfunction and subtle language problems. PD is both chronic and progressive. PD is the most common cause of chronic progressive parkinsonism, a term which refers to the syndrome of tremor, rigidity, bradykinesia and postural instability. PD is also called "primary parkinsonism" or "idiopathic PD". While many forms of parkinsonism are "idiopathic", "secondary" cases may result from toxicity most notably of drugs, head trauma, or other medical disorders. The disease is named after English apothecary James Parkinson, who made a detailed description of the disease in his essay: "An Essay on the Shaking Palsy" (1817).

The term Parkinsonism is used for symptoms of tremor, stiffness, and slowing of movement caused by loss of dopamine. "Parkinson's

disease" is the synonym of "primary parkinsonism", *i.e.*, isolated parkinsonism due to a neurodegenerative process without any secondary systemic cause. In some cases, it would be inaccurate to say that the cause is "unknown", because a small proportion is caused by genetic mutation.

ETIOLOGY:

Most people with Parkinson's disease are described as having idiopathic Parkinson's disease. There are far less common causes of Parkinson's disease including genetic, toxins, head trauma, cerebral anoxia, and drug-induced Parkinson's disease.

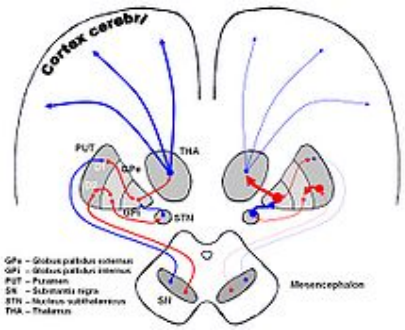
Genetic; Someone who has Parkinson's disease is more likely to have relatives that also have Parkinson's disease. However, the inheritance of Parkinson's disease is usually complex and not due to a single gene defect. A number of specific genetic mutations causing Parkinson's disease have been discovered. Genes identified as of 2008 are Alpha-synuclein (SNCA), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1), parkin (PRKN), leucine-rich repeat kinase 2 (LRRK2 or dardarin) , PINK 1 and DJ-1.With the exception of LRRK2 they account for a small minority of cases of PD.

Toxins; One theory holds that many or even most cases of the disease may result from the combination of a genetically determined vulnerability to environmental toxins along with exposure to those toxins.

The toxins most strongly suspected at present are certain pesticides and transition-series metals such as manganese or iron, especially those that generate reactive oxygen species, and/or bind to neuromelanin.In a longitudinal investigation, individuals who were exposed to pesticides had a 70% higher incidence of PD than individuals who were not exposed.

Head trauma; Head trauma is considered a risk factor for PD since past episodes are reported more frequently by individuals with Parkinson's disease than by others in the population.

PATHOPHYSIOLOGY:



Dopaminergic pathways of the human brain in normal condition (left) and Parkinson's disease (right). Red Arrows indicate suppression of the target, blue arrows indicate stimulation of target structure.

The symptoms of Parkinson's disease result from the greatly reduced activity of pigmented dopamine-secreting (dopaminergic) cells in the pars compacta region of the substantia nigra. These neurons project to

the striatum and their loss leads to alterations in the activity of the neural circuits within the basal ganglia that regulate movement, in essence an inhibition of the direct pathway and excitation of the indirect pathway. The direct pathway facilitates movement and the indirect pathway inhibits movement, thus the loss of these cells leads to a hypokinetic movement disorder. The lack of dopamine results in increased inhibition of the ventral anterior nucleus of the thalamus, which sends excitatory projections to the motor cortex, thus leading to hypokinesia.There are four major dopamine pathways in the brain; the nigrostriatal pathway, referred to above, mediates movement and is the most conspicuously affected in early Parkinson's disease. The other pathways are the mesocortical, the mesolimbic, and the tuberoinfundibular. Disruption of dopamine along the non-striatal pathways likely explains much of the neuropsychiatric pathology associated with Parkinson's disease.

The mechanism by which the brain cells in Parkinson's are lost may consist of an abnormal accumulation of the protein alpha-synuclein bound to ubiquitin in the damaged cells. The alpha-synuclein-ubiquitin complex cannot be directed to the proteasome. This protein accumulation forms proteinaceous cytoplasmic inclusions called Lewy bodies. The latest research on pathogenesis of disease has shown that the death of dopaminergic neurons by alpha-synuclein is due to a defect in the machinery that transports proteins between two major cellular organelles — the endoplasmic reticulum (ER) and the Golgi apparatus.

Excessive accumulations of iron, which are toxic to nerve cells, are also typically observed in conjunction with the protein inclusions. Iron and other transition metals such as copper bind to neuromelanin in the affected neurons of the substantia nigra. Neuromelanin may be acting as a protective agent. The most likely mechanism is generation of reactive oxygen species. Iron also induces aggregation of synuclein by oxidative mechanisms.Similarly, dopamine and the byproducts of dopamine production enhance alpha-synuclein aggregation. The precise mechanism whereby such aggregates of alpha-synuclein damage the cells is not known.

CLINICAL FEATURES:

MOTOR; Four symptoms are considered cardinal in PD: tremor, rigidity, bradykinesia and postural instability.

Tremor; normally has a frequency between 4 and 6 Hz (cycles per second) and is the most apparent and well-known symptom. It is most commonly a rest tremor, maximal when the limb is at rest and disappearing with voluntary movement and sleep. It is a pronation-supination tremor that is described as "pill-rolling". Tremor affects to a greater extent the most distal part of the extremity and is typically unilateral at onset. Though around 30% of PD sufferers do not have tremor at disease onset most of them would develop it along the course of the disease.

Rigidity: defined as joint stiffness and increased muscle tone. In combination with a resting tremor, this produces a ratchety, "cogwheel rigidity" when the limb is passively moved. It may be associated with joint pain, such pain being a frequent initial manifestation of the disease.

Bradykinesia and Akinesia: the former refers to slowness of movement while the latter to the absence of it. It is the most characteristic clinical feature of PD and it produces difficulties not only with the execution of a movement but also with its planning and initiation. The performance of sequential and simultaneous movements is also hindered. Rapid, repetitive movements produce a dysrhythmic and decremental loss of amplitude.

Postural Instability: failure of postural reflexes, along other disease related factors such as orthostatic hypotension or cognitive and sensory changes, which lead to impaired balance and falls.It usually appears in the late stages of PD.

Other motor symptoms include:

Gait and posture disturbances: Shuffling gait: gait is characterized by short steps, with feet barely leaving the ground. Small obstacles tend to cause the patient to trip. Decreased arm-swing.

Turning "en bloc": rather than the usual twisting of the neck and trunk and pivoting on the toes, PD patients keep their neck and trunk rigid, requiring multiple small steps to accomplish a turn.

Camptocormia: stooped, forward-flexed posture. In severe forms, the head and upper shoulders may be bent at a right angle relative to the trunk.

Festination: a combination of stooped posture, imbalance, and short steps. It leads to a gait that gets progressively faster and faster, often ending in a fall.

Gait freezing: also called motor blocks, is a manifestation of akinesia. Gait freezing is characterized by a sudden inability to move the lower extremities which usually lasts less than 10 seconds. It may worsen in tight, cluttered spaces, when attempting to initiate gait or turning around, or when approaching a destination. Freezing improves with treatment and also with behavioral techniques such as marching to command or following a given rhythm.

Dystonia: abnormal, sustained, painful twisting muscle contractions, often affecting the foot and ankle (mainly toe flexion and foot inversion) which often interferes with gait.

Speech and swallowing disturbances; Hypophonia: soft speech. Monotonic speech: Speech quality tends to be soft, hoarse, and monotonous. Festinating speech: excessively rapid, soft, poorly-intelligible speech. Drooling: most likely caused by a weak, infrequent swallow. Dysphagia; paired ability to swallow; which in the case of PD is probably related to an inability to initiate the swallowing reflex or by a too long laryngeal or oesophageal movement. Can lead to aspiration pneumonia.

Other motor symptoms: Fatigue, Hypomimia:a mask-like face, Difficulty rolling in bed or rising from a seated position. Micrographia: small, cramped handwriting. Impaired fine motor dexterity and motor coordination. Impaired gross motor coordination. Akathisia: an unpleasant desire to move. Reemergence of primitive reflexes.

NONMOTOR SYMPTOMS:

Neuropsychiatric symptoms; Depression, apathy, anxiety, panic attacks, anhedonia, attention deficit. hallucination, illusion, delusion (disease or drug induced). Dementia, confusion or delirium (disease and/or drug induced). obsessional and impulsive behaviour(usually drug induced), repetitive behaviour (punding).

Sleep Disorders: Restless legs, Periodic Limb Movements, REM behaviour disorder excessive daytime somnolence. Non REM sleep related Disorder, vivid dreaming, insomnia.

Autonomic symptoms; Bladder disturbances; urgency, nocturia, frequency, hyperhidrosis orthostatic hypotension; Vcoat hanger pain. Sexual dysfunction; hypersexuality, erectile dysfunction, loss of libido. Dry eyes (xerophthalmia) or wet eyes (lacrimation), dry mouth (xerostomia), dribbling of saliva (sialorrhoea).

Gastrointestinal symptoms;(overlap with autonomic)include delayed gastric emptying, ageusia, dysphagia, choking, reflux. vomiting, nausea (usually drug related), constipation, anismus, volvulus, megacolon. incomplete voiding of bowel, faecal incontinence.

Sensory symptoms; are pains, paraesthesia, olfactory disturbance (hyposmia).

Miscellaneous symptoms; like fatigue, diplopia, blurred vision, seborrhoea, weight loss.

Fluctuation related NMS; include pain, mental clouding, anxiety, panic attacks, depression, hallucination, psychosis, screaming, hyperventilation, hypoventilation. Hyperhidrosis, temperature changes, somnolence, restless legs, akathisia. Belching, dysphagia, constipation, anismus, urinary voiding difficulty, altered blood pressure.

A common misconception is that NMS occur only in late or advanced PD. However NMS can first present at any stage of the disease. Several NMS of PD such as olfactory dysfunction, constipation,

depression and erectile dysfunction may predate the motor signs, symptoms and diagnosis of PD by a number of years.NMS may appear early in the course of PD and become prominent as the disease progresses, often dominating the later stages of the diseases. It is likely that some NMS such as olfactory dysfunction in combination with other symptoms such as REM behavioural disorder or constipation may form part of a battery of tests to identify a population at risk of PD, which will be particularly important if and when neuroprotective therapies become available.

Stacy et al found that NMS were common even in patients within 5 years of (motor)disease arrest and they were captured much more frequently with the use of a patient completed Questionnaire (NMS QUEST)than simply in the course of a routine clinic appraisal, including the questions in the Unified Disease Rating Scale(UPDRS). Recent studies using the nonmotor symptoms questionnaire for PD (NMS Quest) have highlighted the significant occurrence of a range of 30 different NMS in PD in comparison with an age matched control group. These occurred across a range of PD patients from early to advanced disease, correlating strongly with advancing disease. In particular many NMS such as dribbling saliva, dysphagia, sexual problems and pain had not been discussed with the doctor before being flagged up by the NMS Quest. The study also highlighted that, irrespective of county of study and disease stage, most PD patients are likely to flag up 9 to 12 different

NMS in the NMS Quest at clinic visit. Additionally, further studies validating the first dedicated scale for NMS of PD, the Parkinson's Disease Nonmotor Scale(NMSS)also indicated a strong relationship between the burden of NMS in PD and health related QoL.

Most NMS are thought to be refractory to current dopaminergic treatment, although this has not been assessed and this view is increasingly challenged. For example, some dopaminergic agonists have been reported to improve depression, REM behaviour and nocturia and apomorphine may help erectlie dysfunction and anismus in PD. Dopominergic agents can alleviate the 'off' period related NMS of PD, such as pain, anxiety and depressed mood. In particular the rapid and reliable onset of action of apomorphine injection or booster can transfer the lives of subjects whose off NMS dominate their lives.

However many NMS may need specific targeted non-dopaminergic treatment and the development of successful therapies for NMS will depend upon accurate reproducible and robust means of quantification, an understanding of their prevalence and evolution with disease progression and their effect on QoL.

DIAGNOSIS:

The diagnosis is based on medical history and neurological examination conducted by interviewing and observing the patient in person using the Unified Parkinson's Disease Rating Scale.

The UPDRS is a scale that was developed as an effort to incorporate elements from existing scales to provide a comprehensive but efficient and flexible means to monitor PD-related disability and impairment. The scale itself has four components, largely derived from preexisting scales that were reviewed and modified by a consortium of movement disorders specialists (Part I, Mentation, Behavior and Mood; Part II, Activities of Daily Living; Part III, Motor; Part IV, Complications).The UPDRS is often accompanied by and reported with such scales as the Schwab and England and Hoehn and Yahr scales, these latter scales are not part of the UPDRS per se. The strengths of the UPDRS are many, and the scale provides a relatively comprehensive assessment of motor aspects of PD. Extensive clinimetric analyses have already been conducted on the UPDRS, providing it both scientific and clinical credibility. The UPDRS is less comprehensive in its assessment of nonmotor features of the disease.

HOEHN and YAHR STAGE:

STAGE O- No signs of disease

1- Unilateral disease

1.5- Unilateral plus axial involvement

2.0- Bilateral disease, without impairment of balance

2.5- Mild bilateral disease, with recovery on pull test

3.0- Mild to moderate bilateral disease, some postural instability, physically independent

4.0- Severe disability, still able to walk or stand unassisted

5.0- Wheelchair bound or bedridden unless aided

IMAGING:

SPECT, FDGPET and fMRI scans are used for diagnosing Parkinson's Disease. Due to this, the disease can be difficult to diagnose accurately, especially in its early stages. Due to symptom overlap with other diseases, only 75% of clinical diagnoses of PD are confirmed to be idiopathic PD at autopsy. Early signs and symptoms of PD may sometimes be dismissed as the effects of normal aging. The physician may need to observe the person for some time until it is apparent that the symptoms are consistently present. However, CT and MRI brain scans of people with PD usually are normal.

TREATMENT:

Parkinson's disease is a chronic disorder that requires broad-based management including patient and family education, support group services, general wellness maintenance, physiotherapy, exercise, and nutrition. At present, there is no cure for PD, but medications or surgery can provide relief from the symptoms.

LEVODOPA: Levodopa remains the most effective medication to improve motor features of PD with the fewest short-term side effects. It effectively ameliorates bradykinesia and rigidity but is variably effective for tremor. Levodopa is combined with the peripheral dopa decarboxylase inhibitor carbidopa to reduce the peripheral metabolism of levodopa to dopamine. This reduces nausea and increases levodopa delivery to the brain, where it is converted to dopamine, stored, and slowly released by remaining dopaminergic neurons.

Carbidopa / levodopa, now available generically, is available as immediate release ([IR] 10/100, 25/100, and 25/250)and controlled release ([CR] 25/100 and 50/200) formulations. Carbidopa / levodopa IR and CR are also available as generics. The initial target dose is typically carbidopa / levodopa IR 25/100administered 3 or 4 times per day, or carbidopa / levodopa CR 50/200 twice a day, although these are more a matter of convention than scientific rigor. Starting carbidopa / levodopa at a dosage of one-half tablet once a day and increasing the daily dose by

one-half tablet every week until the target dose is reached may be helpful to avoid nausea. Although carbidopa / levodopa is usually administered away from meals to achieve the most rapid onset of action and the most reliable effect, if nausea does occur, it can often be reduced by having patients take the dose immediately following a meal. Levodopa alone has a half-life of approximately 60 minutes, and when given with carbidopa it has a half-life of approximately 90 minutes.

As the disease progresses and more dopamine neurons are lost, the duration of clinical benefit shortens to a few hours, and many patients develop choreiform (twisting, turning) movements when levodopa-derived dopamine in the brain is peaking (peak dose dyskinesias). The use of carbidopa / levodopa CR in early disease may be more convenient and require fewer daily doses, but it has not been found to reduce the development of motor fluctuations and dyskinesia compared with carbidopa/levodopa IR.

Parcopa is an orally disintegrating carbidopa / levodopa tablet that dissolves within seconds after being placed on the tongue. Parcopa is convenient for patients because it can be taken with or without water, such as when traveling, and is especially helpful for patients who have swallowing problems. After dissolving, Parcopa is carried in the saliva to the proximal small bowel where it is absorbed. Three strengths of Parcopa are available: carbidopa / levodopa 10/100, 25/100, and 25/250.

Parcopa was approved based on the demonstration of bioequivalence with Sinemet IR and should provide the same clinical benefit and side effects.

COMT INHIBITORS: Levodopa is also metabolized peripherally by catechol-O-methyltransferase(COMT) to produce 3-O-methyldopa (3-OMD). Entacapone is a selective, reversible, peripherally acting COMT inhibitor that is used in conjunction with carbidopa/levodopa to extend the levodopa half-life and allow more levodopa to be delivered to the brain over a longer time. Entacapone is approved as an adjunct to carbidopa/levodopa in patients who experience end-of-dose wearing off. Entacapone is customarily administered with each dose of carbidopa/levodopa. Some patients will notice an orange or brown discoloration of urine, saliva, or sweat.Diarrhea occurs in 4% to 10% of patients treated with entacapone. Hepatotoxicity has not been found to occur with entacapone use, and routine liver monitoring is unnecessary.

Stalevo is a combination of carbidopa, levodopa, and entacapone. Stalevo provides a convenient option for patients who are taking carbidopa / levodopa and entacapone tablets and may be easier to swallow. Stalevo is recommended for use in patients who have end-of-dose wearing off on carbidopa/levodopa IR . In these patients, switching from carbidopa / levodopa to Stalevo is comparable to adding entacapone but with a reduced pill burden. For patients with dyskinesia and those taking greater than 600-mg levodopa per day it is recommended that entacapone should first be added, and if dyskinesia increases, the

levodopa dosage can be reduced. Once stabilized on carbidopa / levodopa plus entacapone, the patient can be switched to the comparable dose Stalevo tablets.

Tolcapone is a selective, centrally and peripherally acting, reversible COMT inhibitor that is used to reduce off time in patients with motor fluctuations on carbidopa / levodopa. Tolcapone extends the levodopa half-life more than entacapone, but because of the potentially fatal side effect of hepatic failure, its use is reserved for patients who cannot be adequately controlled with other PD medications. It is recommended that patients provide written informed consent before the medication is begun, and liver function tests should be monitored for at least 6 months. The new recommendations indicate that liver function tests (serum alanine aminotransferase and aspartate aminotransferase) should be performed every 2 to 4 weeks during the first 6 months of therapy and then periodically according to the clinical judgement of the health care provider.

Patients should discontinue tolcapone if liver enzyme levels exceed twice the upper limit of normal. The usual initial dosage is 100 mg 3 times a day (tid), and it can be increased to 200 mg tid if necessary. Tolcapone should be discontinued if benefit is not observed.Controlled trials indicate that tolcapone improves motor function while allowing reductions in levodopa dosage. One study that evaluated the use of tolcapone in PD patients with motor fluctuations found a daily reduction

in off time of 2.0 hours in patients taking 100 mg tid and 2.5 hours in patients taking 200 mg tid compared with baseline. In comparison, patients taking placebo had only a 0.3-hour reduction in daily off time.

The levodopa boosting effects of the addition of tolcapone are usually evident the day it is added. The main side effect is an increase in dyskinesia. This occurs to a greater extent with tolcapone than with entacapone, and in patients with dyskinesias it is often helpful to reduce the levodopa dose by 25% to 50% when tolcapone is added. Other potential side effects include diarrhea in 10% of patients. The diarrhea can be severe and is usually delayed for 4 to 12 weeks after initiation of therapy and uncommon after 6 months.

DOPAMINE AGONISTS : DAs are effective as monotherapy in early PD to improve motor symptoms and as adjuncts to levodopa in patients with motor fluctuations to reduce off time. They directly stimulate dopamine receptors in the striatum, have relatively long half-lives and are less likely to cause motor complications than levodopa. The oral DAs are less effective than levodopa as the disease progresses but often provide adequate benefit as monotherapy for 1 to 3 years. Additional potential side effects include sleepiness, hallucinations, peripheral edema, hypersexuality, and pathological gambling. Hallucinations generally occur in patients with underlying dementia. Multiple clinical trials have demonstrated that initial treatment with a DA

to which levodopa can be added causes fewer motor fluctuations and dyskinesia than treatment with levodopa alone.

Pramipexole is a nonergot D2/D3 synthetic aminobenzothiazole derivative that is effective as monotherapy in early disease and as an adjunct to levodopa in patients with motor fluctuations. In the Comparison of the Agonist Pramipexole to Levodopa Regarding Emergence of Motor Fluctuations in PD (CALM-PD) study, 301 patients were randomized to receive initial treatment with pramipexole or levodopa and were followed for 4 years. Open-label levodopa could be added as necessary. At study endpoint, patients assigned to levodopa had better motor function than those taking pramipexole. However, only25% of patients initially treated with pramipexole exhibited dyskinesia compared with 54% of patients initially treated with levodopa.

The usual maximum dose of pramipexole is 4.5 mg/d in three divided doses. It is started at a dosage of 0.125 mg tid for a week and then titrated to 0.5 mg tid. Further escalation can be undertaken as necessary. Side effects include somnolence, hallucinations, cognitive dysfunction, and edema. Recent reports indicate that pathological gambling may be associated with DAs, especially pramipexole, usually at high doses. In one review, the incidence of pathological gambling was 1.5% in patients taking pramipexole (mean dosage 4.3 mg/d, range 2 mg/d to 8 mg/d), compared with an overall incidence of 0.05% in patients with PD regardless of therapy. Excessive shopping and hypersexuality are other

forms of impulse control disorders that may occur with DA use. Patients should be warned about these behaviours when DAs are prescribed, and DA dosages may need to be reduced, if these problems emerge.

Ropinirole is a non ergot DA with a strong affinity for D2 receptors. It is effective as monotherapy in early disease and as an adjunct to levodopa in patients with motor fluctuations. One study of ropinirole as monotherapy in patients with early PD found a 24% improvement in motor function in patients taking ropinirole after 6 months compared with a 3% worsening for those patients taking placebo. Ropinirole has also been shown to reduce the development of dyskinesia in early PD patients compared with treatment with levodopa. A 5-year study that randomized patients to initial treatment with ropinirole or levodopa to which levodopa could be added when necessary found that only 20% of patients assigned to ropinirole developed dyskinesia, compared with 45% of patients assigned to levodopa.

These findings indicate that initial dopaminergic treatment with ropinirole leads to a lower incidence of dyskinesia, and levodopa can be added when necessary to control motor symptoms as the disease progresses. The recommended initial dosage for ropinirole is 0.25 mg 3 times daily (total 0.75 mg per day). This can be increased weekly by 0.25-mg increments at each dose. The daily dose can then be increased by 1.5 mg/d after week 4 on a weekly basis up to a dose of 9 mg/d, and then by up to 3 mg/d weekly up to the recommended maximum total daily

dose of 24 mg/d. Side effects include somnolence, hallucinations, peripheral edema, and rarely impulse control disorders.

Pergolide, an ergot DA with strong affinity for D2 receptors, is effective in reducing motor symptoms in PD. Several studies have shown that the use of pergolide permits a significant reduction in levodopa dosage when it is used as adjunct therapy in patients with motor fluctuations compared with placebo.

Pergolide is usually initiated at a dose of 0.05 mg for the first 2 days and increased by 0.1 mg/d or 0.15 mg/d every third day over the next 12 days. Pergolide may then be increased by 0.25 mg/d every third day until an optimal therapeutic dose is achieved. Pergolide is usually aministered in divided doses 3 times per day, and the usual maximum dosage is 3 mg/d to 4 mg/d. Studies have identified an increased frequency of valvular heart disease in patients taking pergolide. This appears to be a potential side effect of all ergot agonists, and the mechanism is believed to be activation of 5-hydroxytryptamine 2B (5-HT2B) receptors. It may therefore be appropriate to obtain early echocardiograms on patients who are receiving pergolide. Pleuropulmonary and retroperitoneal fibrosis can also rarely occur.

Apomorphine is a nonergot DA that is approved as a subcutaneous injection to treat acute intermittent off and hypomobility states in PD as a rescue medication. Originally introduced as a PD drug in the mid-20th

century, its use was initially limited by side effects, including marked nausea. It is now administered with an antiemetic. When injected subcutaneously, its onset of action is approximately 10 to 15 minutes with the effect lasting from 90 to 120 minutes. Side effects of apomorphine include nausea, somnolence, dyskinesia, vomiting, and yawning.

The appropriate dosage for each patient must be determined based on clinical response and side effects. Advanced patients who are considering apomorphine should be pretreated with the antiemetic trimetho benzamide 300 mg tid orally for atleast 3 days. Patients then visit the doctor's office in the off state and receive a test dose of apomorphine 2 mg subcutaneously. Orthostatic blood pressures are measured at 20, 40, and 60 minutes following the first test dose. If the 2-mg dose reverses PD symptoms, this dose is prescribed. If no clinical response occurs, a dose of 4 mg is administered 2 hours after the first dose. If the patient experiences a good clinical response, he or she maybe treated with a dose of 3 mg per injection and may increase this dosage by 1mg increments every few days as needed. Most patients respond to 3 mg to 6 mg of apomorphine.

MAO-B INHIBITORS; Selegiline is a relatively selective, irreversible monoamine oxidase type B (MAO-B) inhibitor that is beneficial as an adjunct to levodopa for patients who have motor fluctuations. It also has modest symptomatic benefit as monotherapy in early PD and has generated interest in possible neuroprotective effects.

The Deprenyl and Tocopherol AntioxidativeTherapy of Parkinsonism. (DATATOP) study demonstrated that selegiline monotherapy in early disease provides modest symptomatic benefit and significantly delays the need for levodopa. Oral selegiline is approved as an adjunct to levodopa in patients who demonstrate a deteriorating response to treatment.

The recommended dosing is 5 mg with breakfast and lunch. Doses later in the day may cause insomnia. At dosages above 10 mg/d, oral selegiline begins to lose its specificity for MAO-B and should therefore usually be avoided because of the risk of tyramine induced hypertensive crisis. Selegiline is used with caution with selective serotonin reuptake inhibitor(SSRI) antidepressants to avoid the serotonin syndrome characterized by agitation, restlessness, rigidity, hyperreflexia, shivering, autonomic instability,flushing, fever, nausea, diarrhea, diaphoresis, myoclonus, coma, and rarely rhabdomyolysis and death. The Zydis selegiline formulation is a wafer that dissolves and is absorbed in the mouth, thereby bypassing hepatic first-pass metabolism. This method of absorption may allow for higher plasma concentrations of selegiline compared with oral selegiline before MAO-A in the gut is inhibited.

Rasagiline is an irreversible MAO-B inhibitor that has been shown to effectively treat symptoms of PD when used as monotherapy in patients with early PD and as an adjunct to levodopa in patients with motor fluctuations. It appears to have greater symptomatic efficacy than oral selegiline. Rasagiline provides neuroprotection in a number of cell

and animal models and is free of amphetamine metabolites, which have been demonstrated to interfere with neuroprotective effects of selegiline.

Rasagiline was evaluated as monotherapy in early disease in the Rasagiline Mesylate (TVP-1012) in Early Monotherapy for PD Out patients (TEMPO) study. Results from the 6-month double-blind phase demonstrated that rasagiline significantly improves Unified Parkinson Disease Rating Scale (UPDRS) scores compared with placebo and that side effects were similar to placebo. The trial also incorporated a delayed-start component, and patients who initially received placebo for the first 6 months were treated with rasagiline 2 mg/d for the next 6 months while rasagiline treated patients continued on it. After 1 year, patients treated with rasagiline from the beginning of the study had less worsening in total UPDRS scores compared with patients who started rasagiline after 6 months of placebo. This result suggests that rasagiline might have benefit in slowing disease progression,but further investigation is needed.

Another trial, Parkinson’s Rasagiline: Efficacyand Safety in the Treatment of off (PRESTO), evaluated the effect of rasagiline as adjunct therapy in levodopa treated patients with motor fluctuations. Another study found that both rasagiline once daily and entacapone administered with each levodopa dose significantly decreased off time and increased on time compared with placebo. Although no dietary restrictions were included in the pivotal clinical trials, the USFDA has recommended that

patients on rasagiline avoid foods that are high in tyramine, such as redwine, aged cheeses, and aged meats.

ANTICHOLINERGIC MEDICATIONS:Anticholinergic medications such as trihexyphenidyl and benztropine are effective for reducing tremor in some patients but have little effect on bradykinesia and rigidity. Their use is limited by side effects, including confusion, hallucinations,dry mouth and eyes, urinary retention, ocular accommodation abnormalities, sweating, and tachycardia. These drugs must be used with caution in older adults and in patients with glaucoma.

AMANTIDINE : is an antiviral medication that provides mild benefit in treating PD signs and symptoms. It also symptomatically reduces levodopa-induced peak-dose dyskinesia. It may act by direct stimulation of dopamine receptors and by inhibiting dopamine reuptake. Amantadine is administered at a dose of 100 mg bid or tid. It should be used cautiously in elderly patients and in those with dementia, as it can cause or worsen hallucinations.

SURGERY AND DEEP BRAIN STIMULATION:

After decades of lesion therapy, it was discovered that chronic electrical stimulation had significant and lasting benefits for the treatment of movement disorders. Deep brain stimulation (DBS) was introduced in 1987 by Benabid and colleagues for the treatment of tremor in patients with Parkinson’s disease (PD). A few short years after its introduction,

high-frequency stimulation (HFS) of the globus pallidus interna (GPi), and later the subthalamic nucleus (STN), was noted to dramatically improve the symptoms of idiopathic PD. DBS is now US Food and Drug Administration (USFDA)-approved for the treatment of PD. The treatment is now considered standard of care for a subset of medically refractory patients with PD. DBS is often compared with brain lesioning (pallidotomy, thalamotomy, subthalamotomy). The main advantages of DBS over lesioning include reversibility of the procedure, the ability to program the stimulator, and the ability to perform bilateral procedures without inducing pseudobulbar and other deficits.

Currently STN and GPi are the preferred brain targets for the treatment of medication-refractory PD. While each has advantages, particularly in the treatment of specific symptoms, there remains no consensus as to which target is superior. Both have the potential to improve the cardinal features of PD, including tremor, bradykinesia, rigidity, gait dysfunction, and postural instability. Additionally, both are known to reduce on–off fluctuations, dyskinesias, and dystonia. While some studies have concluded that STN DBS was slightly superior in improving motor scores, tremor, and bradykinesia, others have not shown significant differences.

The marked clinical improvement usually seen with bilateral STN stimulation. Bilateral STN stimulation does seem to have an advantage over GPi in allowing medication reduction, which can also indirectly

result in a long-term cost savings. Because of its smaller size, STN has on average a lower voltage requirement, which may provide an advantage in terms of improving battery life. Dyskinesia management, however, may be slightly superior with GPi stimulation, which provides a more direct anti dyskinetic effect.

Additionally, many mood and cognitive side effects have been reported with STN DBS, and their presence has raised questions regarding safety in individual patients, particularly elderly persons and those with cognitive impairment. To date, no head-to-head trials on which to base selection of target have been done. Both targets are USFDA approved, and both are efficacious.

The thalamic target (ventralis intermedius nucleus or VIM) has been found to be efficacious in alleviating PD tremor but has not been effective in treating other PD symptoms, including bradykinesia, rigidity, dyskinesias, and postural instability. VIM nucleus DBS has been demonstrated to be superior inefficacy in improving activities of daily living in comparison with unilateral thalamotomy for PD tremor, although there may be reasons to opt for lesion therapy. Stimulation of the thalamus has also been reported to result in delayed tremor rebound. Long-lasting effect on tremor in PD with VIM nucleus DBS has been demonstrated however, the lack of effect on other PD symptoms has greatly curbed the use of this target for PD. Recent reports suggest the paramedian pontine nucleus as a possible target for improvement of gait

in parkinsonian patients. If it can be shown that this target improves levodopa-unresponsive gait symptoms, it may prove an important consideration for future trials.

DBS has proven efficacy in the treatment of the major motor symptoms of PD, including bradykinesia, rigidity, tremor, gait dysfunction, and postural instability. Long-term studies have demonstrated that the effects of DBS are sustained. Perhaps the most important point to remember when considering the referral of a patient is that only those symptoms that respond to levodopa(when the patient is in the best optimized on state) will respond to DBS. The main exception to this rule is medication-refractory tremor, which can be well controlled with DBS. No consensus has been formed as to the appropriate timing for DBS surgery, but, in general, the procedure should be reserved for medication-responsive symptoms in non demented patients with PD, who may also have tremor or on–off fluctuations. In practical terms, the patient under consideration for a surgical referral should experience one or several of the following difficulties:

Motor fluctuations are seen in advanced PD, usually following 5 years or more of dopaminergic therapy. Many types of fluctuations have been described. The most common and the earliest to appear are wearing off of medication doses (predictable worsening of the parkinsonism or reaching the off state because the current dose‘ ‘wears off’’ prior to the next scheduled dose of levodopa). As the disease progresses, these off

states may become more unpredictable, and doses may last for shorter intervals. Patients may also experience delayed ons (the period between ingesting the dose of levodopa and the appearance of its positive effects), dose failures (when a dose of levodopa fails to produce any effect), on–off state(fluctuating between the on and off states), or sudden offs (an unpredictable off state that may be unrelated to the timing of the levodopa dose). A 5-year follow-up study of DBS has shown significant improvement in off-medication motor scores. Patients report a significant portion of the waking day in an off-medication state.

Dyskinesias become disabling and limit levodopa dosage. DBS can decrease the severity of disability related to dyskinesias. Quality of life is severely affected as a result of PD, and patients have levodopa - responsive symptoms. Quality of life scores have shown an improvement with DBS in many studies. The disease itself might not be advanced, but if the patient has disabling medication-refractory tremor (dopamine agonists, anticholinergics, and combinations have been tried) affecting activities of daily living, DBS may be indicated.

TREATMENT OF NONMOTOR SYMPTOMS:

SLEEP DISORDERS: Excessive daytime sleepiness; (EDS) commonly occurs in PD and frequently adversely affects quality of life.EDS can be caused by the disease itself, medications, or sleep disorders. Predictors of EDS in PD include increasing age, advanced disease, and higher dosages of dopaminergic medications. DAs in particular are a common cause of EDS in patients with PD. Acareful medication review and sleep history are warranted for patients with EDS. If a medication that might be causing EDS is identified, it can be reduced or discontinued as feasible. If no medication likely to cause sleepiness is identified, if EDS persists despite medication adjustments, or if the sleep history is suspicious for a sleep disorder, polysomnographic evaluation of sleep should be undertaken. If no treatable sleep disorder is identified, treatment with modafinil or other wake-promoting agents can be considered. The dose range of modafinil in these studies was 200 mg/d to 400 mg/d.

Insomnia; can be treated by having the patient adhere to a consistent sleep schedule, attempt to avoid daytime napping, and abstain from alcohol, caffeine, tobacco, and other stimulants in the evening hours. A review of all current medications is warranted to identify those that might be causing insomnia, such as bronchodilators, stimulants, antidepressants, and weight-loss medications. If night time awakenings are related to parkinsonian motor symptoms, a bedtime dose of a DA,

carbidopa / levodopa CR, or carbidopa / levodopa-entacapone (Stalevo) may be helpful. A carbidopa / levodopa IR dose may provide relief if the patient awakens at night and cannot get back to sleep because medications have worn off. If necessary, injections of subcutaneous apomorphine may be considered. If insomnia is related to nocturia, anticholinergic medications such as tolterodine at bedtime may be helpful to reduce bladder spasms. Depression and anxiety should be treated. Some patients may require the use of hypnotics, such as zolpidem, or trazadone to treat insomnia.

VIVID DREAMS AND HALLUCINATIONS; Vivid dreams are often a precursor to frank hallucinations. Hallucinations are usually triggered by dopaminergic medications in patients with underlying dementia. In such patients, it is usually helpful to reduce or eliminate DAs and minor PD medications, including amantadine and perhaps anticholinergics and MAO-B inhibitors. Hallucinations commonly respond to the addition of an atypical neuroleptic such as quetiapine or clozapine at bedtime. Quetiapine is usually the medication of choice because unlike clozapine, blood monitoring is not required.

REM BEHAVIOUR DISORDER: RBD is characterized by loss of atonia during REM sleep when dreaming occurs. This leads to an ‘‘acting out of dreams,’’ including sleep talking, shouting, and intense, sometimes violent, movements. Patients may inadvertently injure their bed partners by punching or choking them. RBD has been reported in 25% to 50% of

patients with PD and can precede the onset of PD by several years. Clonazepam can be used in dosages of 0.5 mg to 2.0 mg at bedtime to treat RBD.

RESTLESS LEGS SYNDROME : Restless legs syndrome occurs in approximately 20% of patients with PD.DAs, including ropinirole and pramipexole, may be used to treat.

SLEEP APNEA: Obstructive sleep apnea occurs in about 20% of patients with PD and is defined by intermittently absent or reduced airflow during sleep despite respiratory effort. Treatment usually consists of wearing an airflow mask (continuous positive airway pressure).

FATIGUE; Fatigue is characterized by a feeling of lack of energy. Some patients appear to have fatigue related to depression and improve with antidepressant treatment. Others may improve with initiation of antiparkinsonian medications. Treatments for fatigue include modafinil and other stimulants.

ORTHOSTATIC HYPOTENSION; Treatment consists of adequate hydration with eight or more glasses of fluid each day, the liberal addition of salt to the diet (up to 150 mEq to 250 mEq), and the use of mineralocorticoids, such as fludrocortisone, to increase intravascular volume. The initial dose of fludrocortisone is 0.1 mg once or twice a day, which can be increased to 0.3 mg to 0.6 mg per day if needed. Midodrine is a peripherally acting alpha1agonist that produces

arteriole and venous capacitance vessel vasoconstriction. The initial dosage of midodrine is 2.5 mg twice a day(bid) or tid with a maintenance doe of up to 30 mg/d to 40 mg/d in divided doses.

CONSTIPATION; PD have delayed colonic transit time compared with non-PD controls as well as decreased basal anal sphincter pressures and hypercontractile external sphincter response. The disease process itself may affect the enteric nervous system as Lewy bodies have been found in the myenteric plexus of the colon and in the dorsal group of the nucleus intermediolateralis of the third sacral segment of the spinal cord. A paradoxical contraction of the striated sphincter muscles during defecation called anismus may occur in patients with PD and is considered to be a focal dystonia.

Treatment of constipation in PD starts with dietary change to include more fruits, vegetables, and bran products. Medications that inhibit gastric motility and promote gastrointestinal dryness, such as anticholinergics, should be discontinued as feasible. If this is ineffective, medical management includes polyethyleneglycol, an osmotic agent that softens the stool and increases the frequency of bowel movements by causing water to be retained in the stool. The recommended dose is 17 g or one heaping tablespoon of powder per day in 8 ounces of liquid. Stool softeners can often help to relieve constipation in PD as well.

One controlled study found that tegaserod, a prokinetic agent, provides modest improvement in constipation. Two open-label studies found that mosapride, a selective 5-HT4 agonist, improves constipation, but controlled studies are lacking. Lactulose may be needed for patients with refractory constipation. For cases of anismus, botulinum toxin injections may be considered(30 units of botulinum toxin into two sites on the puborectalis muscle).

DYSPHAGIA; Patients with PD have increased oropharyngeal transit time, and Lewy bodies have been found in the myenteric plexus in the esophagus in dysphagic PD patients. Non–dopamine related abnormalities in the pedunculopontine nucleus or related structures in the medulla may also cause swallowing difficulties. optimal treatment with levodopa can improve swallowing, although some patients may need to eliminate hard foods from the diet. Liquids may need to be thickened, and patients should swallow sitting upright.

URINARY INCONTINENCE : Patients with PD may experience urinary incontinence. Detrusor hyperreflexia can result in urinary frequency, urgency, and nocturia, and dopamine deficiency has been implicated as a cause for urinary incontinence in PD. Patients who report urinary incontinence should undergo a urological evaluation, including cystometric studies, to exclude other causes of urinary symptoms. Treatment options include a reduction in fluids in the evening to reduce nocturia and anticholinergic medication such as tolterodine tartrate,

oxybutyninchloride, or propantheline bromide. Another option is the intranasal administration of desmopressin at bedtime to decrease urine production overnight.

DROOLING; Drooling in PD is caused by saliva pooling in the mouth secondary to swallowing difficulties rather than an increased production of saliva. Siallorhea can lead to aspiration. Treatment includes anticholinergic medications, such as glycopyrrolate. For some patients, increased dopaminergic therapy may reduce drooling by improving swallowing.

SEXUAL DYSFUNCTION: Sexual dysfunction is a complex problem in PD and can manifest as difficulty achieving or maintaining erection, loss of sexual interest, or occasionally hypersexuality from dopaminergic medications. Sexual dysfunction affects both men and women with PD. Reports of sexual dysfunction warrant an evaluation by a urologist and cessation of medications such as propranolol and other antihypertensives that can contribute to the condition. Depression as a possible cause of sexual dysfunction must also be addressed. Sildenafil, a potent inhibitor of phosphodiesterase type 5, may be useful in treating erectile dysfunction.

DEPRESSION: Depression is estimated to affect as many as 50% of patients with PD and is more common than in age-matched non-PD controls. Depression in PD is associated with dysphoria and sadness, and less by self-blame and guilt. It may affect patients prior to the onset of motor symptoms and may prove to be a preclinical marker of the disease.

The exact cause of depression in PD is unknown. Antidepressants, including tricyclics and SSRIs, have been found to improve depression in patients with PD, and the DA pramipexole may also have antidepressant efficacy.

DEMENTIA; Dementia probably affects close to 40% of patients with PD and usually emerges later in the course of the disease. Dementia in PD is associated with longer disease duration and older age at onset and is a risk factor for nursing home placement. Patients with dementia have short-term memory deficits but may also have difficulty with verbal fluency and personality and behavioral changes. Rivastigmine, a cholinesterase inhibitor, is now approved for use in treating dementia in PD. In a study of donepezil, at dosages of 5 mg/d to 10 mg/d, improvements occurred in the Mini-Mental State Examination and Clinical Global Impression scale compared with placebo. Galantamine may also improve cognitive dysfunction in PD.

PSYCHOSIS; Occurs in 30% of patients. Unfortunately, many medications that are used to treat motor dysfunction in PD, including amantadine, DAs, and to a lesser extent anticholinergics, levodopa, COMT inhibitors, and MAO-B inhibitors, can exacerbate psychosis and may need to be discontinued or reduced if psychosis occurs. Quetiapine and clozapine have less parkinsonian side effects than other atypical or classical antipsychotics and are effective in treating psychosis symptoms, usually at relatively low doses(12.5 mg/d to 150 mg/d for quetiapine and 12.5 mg/d to 75 mg/d for clozapine).

OBSERVATION & RESULTS:

This study included 100 patients with Idiopathic Parkinson's Disease.

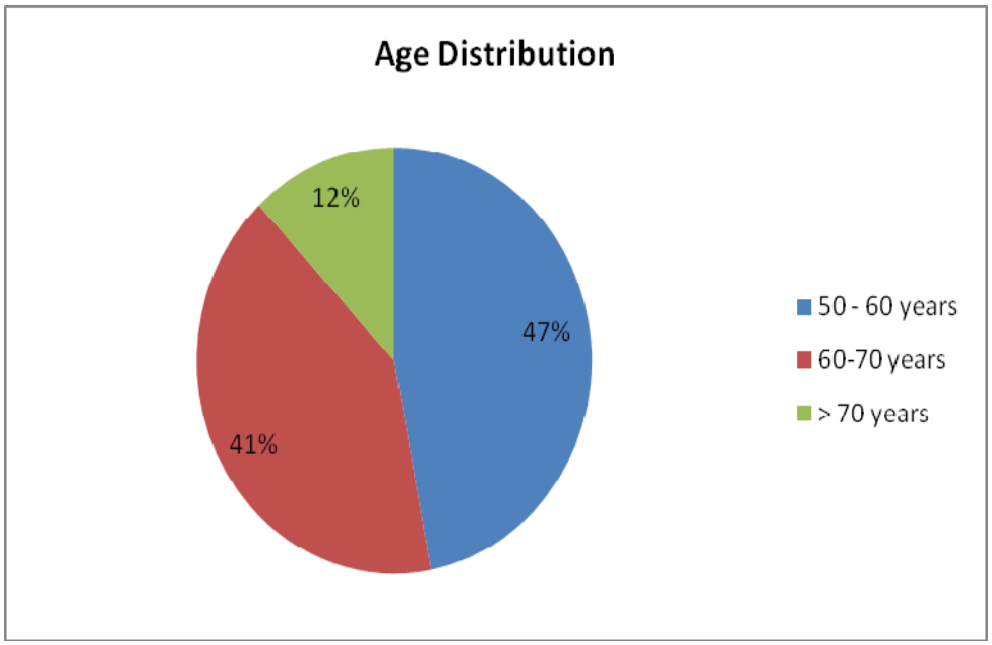
AGE DISTRBUTION:

The number of patients in the

age group between 50 -60 years - 47

age group between 60-70 years - 41

age group > 70 years - 12



SEX DISTRIBUTION:

There were 75 males and 25 females.

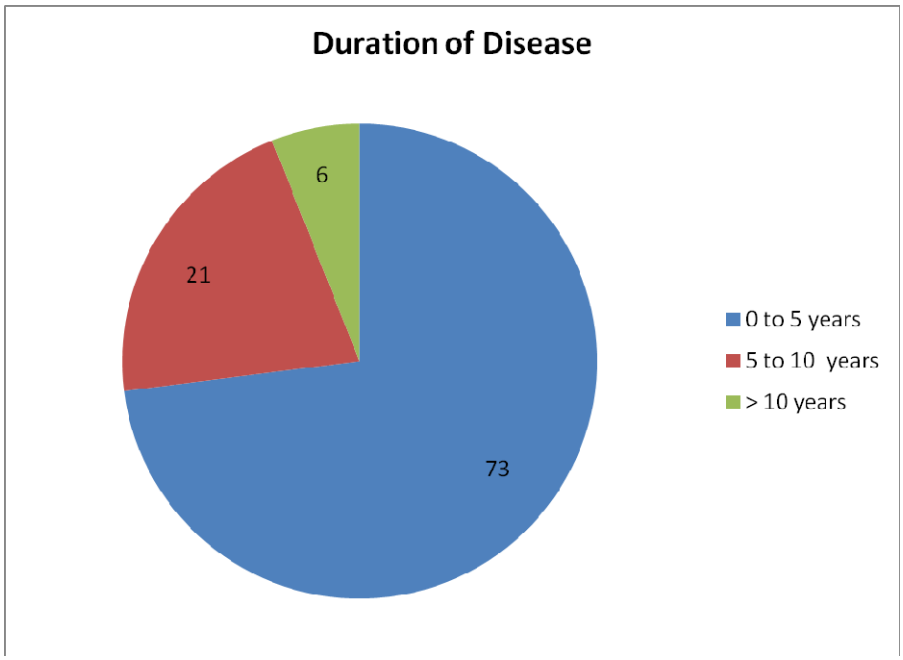
DURATION OF DISEASE:

The number of patients with the

duration of the disease from 0-5 years - 73

duration of the disease from 5-10 years - 21

duration of the disease > 10 years - 6



STAGE OF DISEASE:

Based on the Hoehn and Yahr Staging;

number of patients in Stage 1 - 24

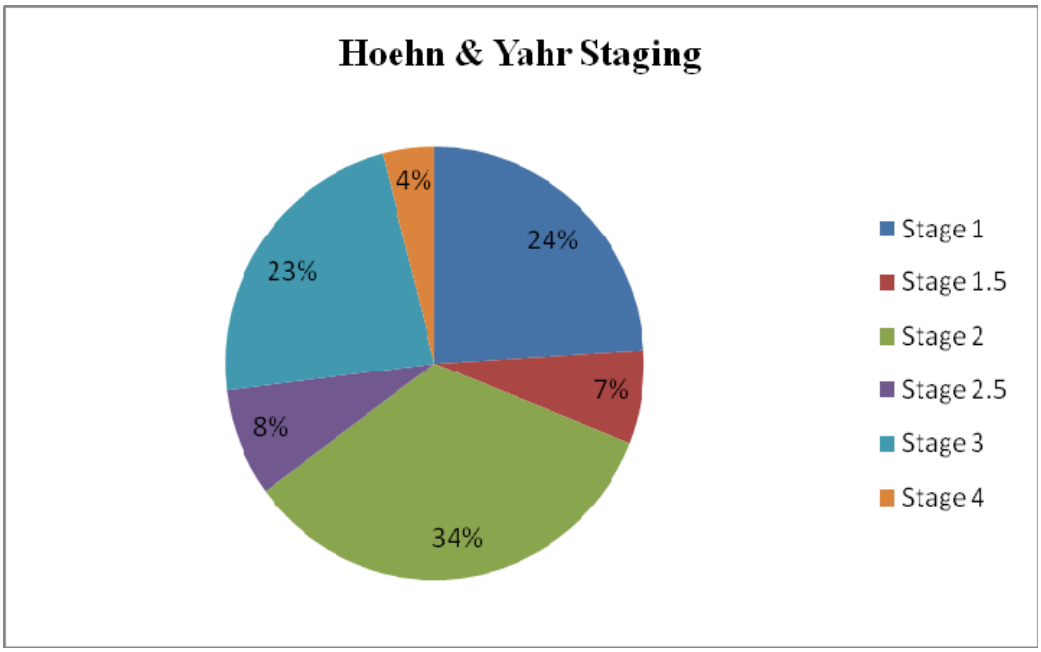
number of patients in Stage 1.5 - 7

number of patients in Stage 2 - 34

number of patients in Stage 2.5 - 8

number of patients in Stage 3 - 23

number of patients in Stage 4 - 4



PREVALENCE OF NON-MOTOR SYMPTOMS IN THE STUDY COHORT: The prevalence of NMS were;

Drooling-37%

Disturbances in taste and smell-27%

Swallowing difficulty-24%

Constipation-50%

Urgency-47%

Nocturia-58%

Dizziness-34%

Pains-28%

Dreams-23%

Insomnia-35%

Sleepiness-20%

Memory-33%

Anxiety-22%

Depression-34%

Hallucination-15%

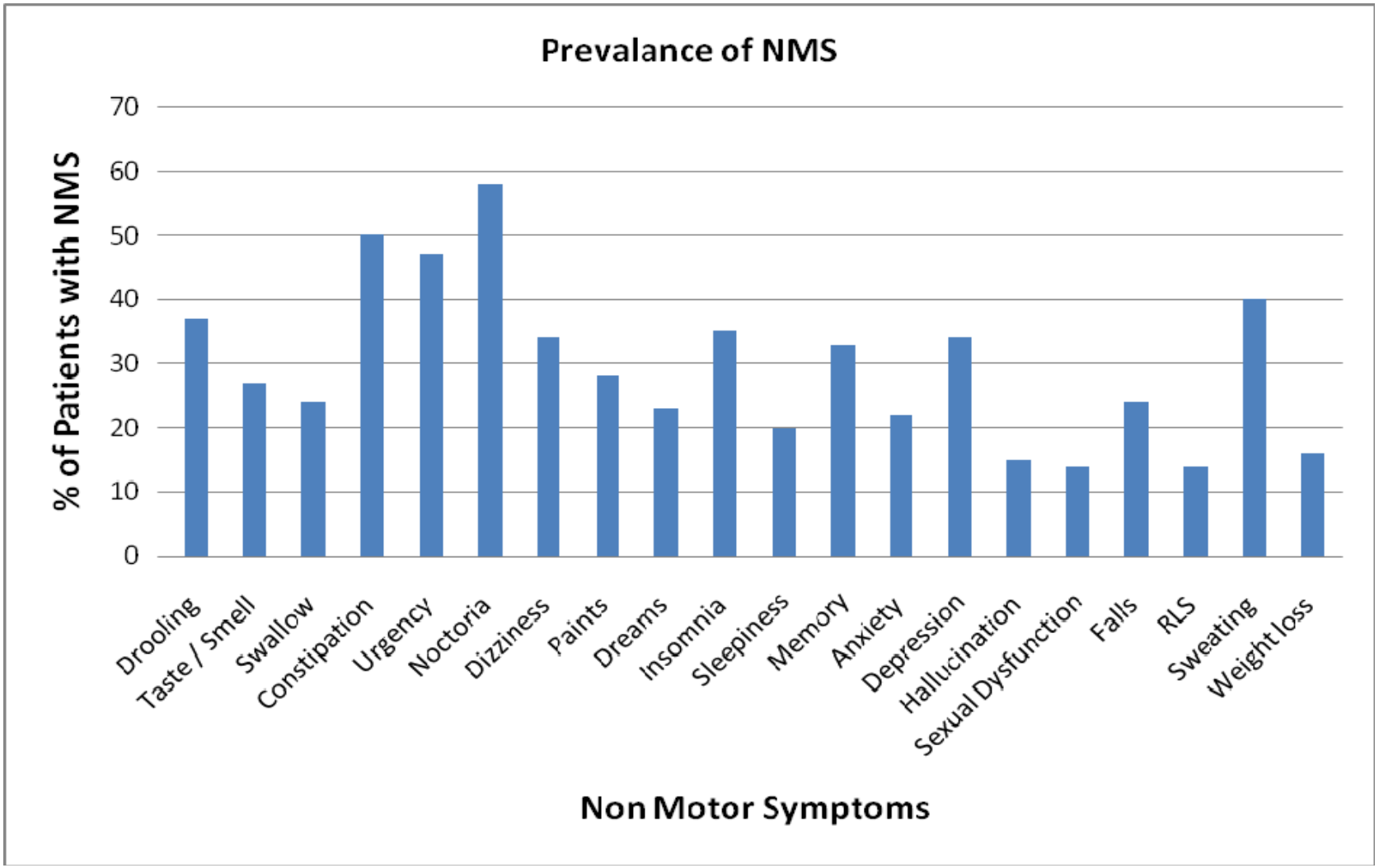
Sexual Dysfunction-14%

Falls-24%

Restless leg syndrome-14%

Sweating-40%

Weight loss-16%


Prevalance of NMS
% of Patients with NMS
70
60
50
40
30
20
10
0
Drooling
Taste / Smell
Swallow
Constipation
Urgency
Noctoria
Dizziness
Paints
Dreams
Insomnia
Sleepiness
Memory
Anxiety
Depression
Hallucination
Sexual Dysfunction
Falls
RLS
Sweating
Weight loss
Non Motor Symptoms

The prevalence of NMS across the various stages of Idiopathic Parkinson's disease are ;

The number of NMS in Stages 1 and 1.5 were less than 5(range of 2-3)

The number of NMS in Stages 2 and 2.5 were in the range of 5 and 7.

The number of NMS in Stages 3 and 4 were between 9 and 12.

The patients in Hoehn and Yahr Stages 1 to 1.5 had duration of disease ranging between 6 months and 2 years. Those in Stages 2 and 2.5 had duration of disease between 2 and 5 years.Patients in Stages 3 and 4 had duration of disease ranging between 5 and 15 years.

DISCUSSION

Chaudhari K R,Martinez Martin P,Schapira AHV, et al (49) from the Unit of Neuro Epidemiology of Carlos Institute of Health, Madrid, Spain have done an International Multicentre Pilot Study of the first comprehensive self completed non motor symptoms questionnaire for Parkinson Disease. They have studied the prevalence of NMS in 545 patients using the NMS Quest. The results were Dribbling - 40%, Disturbances in taste / smell-29%, swallow- 28%, constipation-50%,urgency - 53%, nocturia - 60%, pains - 27%, memory-43%, hallucination-20%, depression - 45%, anxiety - 42%, sexual dysfunction-30%, dizziness-35%, falls - 25%, sleepiness - 29%, insomnia-43%, dreams - 34%, RLS - 39%, sweating - 15%, weight loss - 15%.

Our study has shown higher prevalence of NMS like Nocturia (58%), urgency (47%) and constipation(50%).This compares with Chaudhari et al which has also shown higher prevalence of these symptoms namely Nocturia (60%),urgency (53%) and constipation (50%). The next prevalent NMS were Insomnia (35%), Depression (34%) memory (33%), dreams (23%), anxiety (22%), sleepiness (20%) and hallucinations (15%). These were less compared to Chaudhari et al which has documented a higher prevalence of the same, namely Insomnia (43%), memory (43%), Depression (45%) dreams (34%), anxiety (42%), sleepiness (29%), hallucinations (20%).

Dizziness was reported in 34%,swallowing difficulty in 24%,falls in 24% which has almost the same as reported by Chaudhari et al. Sexual Dysfunction was reported in14% patients as against 30% by Chaudhari et al. Sweating was prevalent in 40% as against 15% reported by Chaudhari et al.RLS was reported in 14% which was 39% in Chaudhari at al. Pain was prevalent in 28%,and weight loss in 16% which is same when compared with Chaudhari et al.

The most prevalent NMS were Autonomic Symptoms namely Nocturia urgency, constipation, sweating, dizziness and drooling. This was followed by Neuropsychiatric symptoms like memory disturbances, depression, anxiety and hallucinations and sleep disturbances which include insomnia, sleepiness and dreams. Pains and weight loss were also prevalent. Diplopia, delusions, bowel and bladder incontinence were reported in a small percentage of patients.

The prevalence of NMS increased with the severity and duration of the disease. The number of NMS ranged between 2 to 3 in stages 1 and 1.5, increased to 5 to 7 in stages 2 and 2.5 and ranged between 9 to 12 in stages 3 and 4.The number of NMS were less when the duration of the disease was less than 2 years and increased with the duration of the disease. It was maximum reported when the duration of the disease was more than 5 years.

In the Indian context, Prevalence of NMS in PD has been carried out at NIMS, Hyderabad, Andhra Pradesh, India. Here the patients had NMS scores between 6 to 20. The most common symptoms identified were dribbling of saliva, swallowing difficulty, urinary urgency, sexual dysfunction, unexplained pains, anxiety, dreams, insomnia, sweating, memory disturbances and falls. Alteration in taste and smell, bowel and urinary incontinence, change in weight and hallucinations were seen in fewer patients.

In another study carried out at the Comprehensive Care Centre For Movement Disorders, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Tiruvananthapuram, Kerala, NMS was assessed by the NMS Scale (9 domains) in 100 consecutive PD patients. The Mood / cognition domain was most frequently involved (84.2%), while the cardiovascular domain was the least affected (22.4%). Four of the domains namely, cardiovascular, perceptual problems, hallucinations, gastrointestinal and urinary showed significant correlation with the duration of the disease and severity of PD. There was a significant correlation between the overall severity of NMS and duration of disease and severity of PD.

Dagmar Verban etal (50) from the Department of Neurology, Leiden University Medical centre, The Netherlands 2007 has characterised these non motor domains in patients of the Profiling Parkinson's Disease (PROPARK) cohort and describes their relation with

other domains of the disease as well as their impact on disability and quality of life. Of the domains evaluated olfaction is the only domain that seemed unrelated to any of the other impairment domains. All other nonmotor symptoms were related to symptoms of other domains. The strongest relation was found between night time sleep problems and depressive symptoms and between psychotic and autonomic symptoms.

The relation found between the different impairment domains may emerge through different causes. First two domains may be related because of a shared underlying mechanism that is inherent to the disease or may be induced by medication or by a combination of both. Second a relation between impairment domains may emerge because different brain regions are simultaneously affected by the disease process. The pathological staging system of Braak, in which the upper brainstem, midbrain and limbic system become involved as the disease progresses, may explain the co-occurrence of features from two different domains. Of the nonmotor domains in PD depressive symptoms and autonomic dysfunction were the most important contributors to HRQoL. Our study has also demonstrated relation between insomnia and depression.

CONCLUSION

(1) Nonmotor symptoms are prevalent across all stages of Parkinson's Disease.

(2) The most prevalent ones were Autonomic which includes Constipation, Nocturia, Urgency and sweating. This was followed by insomnia, depression and memory disturbances. Dizziness, Drooling, Falls and unexplained pains were also significantly reported.

(3) The number of NMS increased as the disease severity progressed. The number of NMS in stages 1 and 1.5 were the least. It increased through stages 2 and 2.5 and were highest reported in stages 3 and 4.

(4) The number of NMS also correlated with the duration of the disease. The number of NMS were least when the duration was less than 2 years, increasing as the duration increased and maximum reported when duration was more than 5 years.

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Unified Parkinson's Disease Rating Scale

Name											Unit Number									
		Date																		
	DOPA mg/day	hrs DOPA lasts																		
			On	Off	On	Off	On	Off	On	Off	On	Off	On	Off	On	Off	On	Off	On	Off
1	Mentation																			
2	Thought Disorder																			
3	Depression																			
4	Motivation/Initiative																			
	Subtotal 1–4 (maximum=16)																			
5	Speech																			
6	Salivation																			
7	Swallowing																			
8	Handwriting																			
9	Cutting food																			
10	Dressing																			
11	Hygiene																			
12	Turning in bed																			
13	Falling																			
14	Freezing																			
15	Walking																			
16	Tremor																			
17	Sensory symptoms																			
	Subtotal 5–17 (maximum=52)																			
18	Speech																			
19	Facial expression																			
20	Tremor at rest: face, lips, chin																			
	Hands:	right																		
		left																		
	Feet:	right																		
		left																		
21	Action tremor:	right																		
		left																		
22	Rigidity:	neck																		
	Upper extremity:	right																		
		left																		
	Lower extremity:	right																		
		left																		

		Date																	
			On	Off	On	Off	On	Off	On	Off	On	Off	On	Off	On	Off	On	Off
23	Finger taps:	right																
		left																
24	Hand grips:	right																
		left																
25	Hand pronate/supinate:	right																
		left																
26	Leg agility:	right																
		left																
27	Arise from chair																	
28	Posture																	
29	Gait																	
30	Postural stability																	
31	Body bradykinesia																	
	Sub-total: 18–31 (maximum=108)																	
	Total points: 1–31 (maximum=176)																	
32	Dyskinesia (duration)																	
33	Dyskinesia (disability)																	
34	Dyskinesia (pain)																	
35	Early morning dystonia																	
36	"Offs" (predictable)																	
37	"Offs" (unpredictable)																	
38	"Offs" (sudden)																	
39	"Offs" (duration)																	
40	Anorexia, nausea, vomiting																	
41	Sleep disturbance																	
42	Symptomatic orthostasis																	
	Blood Pressure:	seated																
		supine																
		standing																
	Weight																	
	Pulse:	seated																
		standing																
	Name of Examiner ▸																	

		Best	Worst	Best	Worst	Best	Worst	Best	Worst	Best	Worst	Best	Worst	Best	Worst	Best	Worst
	Hoehn & Yahr Stage																
	% ADL Score (PD)																
	% ADL (with dyskinesia)																

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PD NMS QUESTIONNAIRE

Name: ..... Date: ..... Age: .....

Centre ID: Male ☐ Female ☐

	Yes	No
1. Dribbling of saliva during the daytime	☐	☐
2. Loss or change in your ability to taste or smell	☐	☐
3. Difficulty swallowing food or drink or problems with choking	☐	☐
4. Vomiting or feelings of sickness (nausea)	☐	☐
5. Constipation (less than 3 bowel movements a week) or having to strain to pass a stool (faeces)	☐	☐
6. Bowel (fecal) incontinence	☐	☐
7. Feeling that your bowel emptying is incomplete after having been to the toilet	☐	☐
8. A sense of urgency to pass urine makes you rush to the toilet	☐	☐
9. Getting up regularly at night to pass urine	☐	☐
10. Unexplained pains (not due to known conditions such as arthritis)	☐	☐
11. Unexplained change in weight (not due to change in diet)	☐	☐
12. Problems remembering things that have happened recently or forgetting to do things	☐	☐
13. Loss of interest in what is happening around you or doing things	☐	☐
14. Seeing or hearing things that you know or are told are not there	☐	☐
15. Difficulty concentrating or staying focussed	☐	☐
16. Feeling sad, 'low' or 'blue'	☐	☐
17. Feeling anxious, frightened or panicky	☐	☐
18. Feeling less interested in sex or more interested in sex	☐	☐
19. Finding it difficult to have sex when you try	☐	☐
20. Feeling light headed, dizzy or weak standing from sitting or lying	☐	☐
21. Falling	☐	☐
22. Finding it difficult to stay awake during activities such as working, driving or eating	☐	☐
23. Difficulty getting to sleep at night or staying asleep at night	☐	☐
24. Intense, vivid dreams or frightening dreams	☐	☐
25. Talking or moving about in your sleep as if you are 'acting' out a dream	☐	☐
26. Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move	☐	☐
27. Swelling of your legs	☐	☐
28. Excessive sweating	☐	☐
29. Double vision	☐	☐
30. Believing things are happening to you that other people say are not true	☐	☐

MASTER CHART

S.No	Age	Sex	Duration of Disease	UPDRS Score	Hoehn & Yahr stage	NON-MOTOR SYMPTOMS																			
						Drooling	Taste / Smell	Swallow	Constipation	Urgency	Nocturia	Dizziness	Pains	Dreams	Insonmia	Sleepiness	Memory	Anxiety	Depression	Hallucination	Sexual dysfunction	Falls	RLS	Sweating	Weight Loss
1	56	M	5	49	3	Y				y	y	y		y	y	y	y		y	*y*		y		y	
2	66	M	2	30	1.5		y		y				y		y										
3	59	M	1	27	1		y				y								y						
4	65	M	2	23	2	y			y	y	y													y	
5	69	F	4	42	1.5				y	y	y	y													y
6	60	F	9	52	3	y		y	y	y				y		y	y		y			y		y	
7	62	M	4	41	2		y			y	y		y					y			y				
8	60	M	2	25	1.5								y				y		y						
9	53	M	2	52	3	y	y		y	y	y		y	y						y		y		y	
10	64	F	6	54	3	y		y	y	y	y	y			y	y		y				y			
11	54	M	2	29	1		y				y								y						
12	51	F	2	30	1				y	y	y														
13	65	M	4	44	2	y			y		y		y					y							
14	50	F	7	49	3	y		y	y		y	y					y			y	y	y		y	y
15	52	F	4	52	2				y		y				y				y					y	
16	46	M	2	51	3	y	y	y	y	y	y	y					y		y			y		y	
17	52	F	8	44	2				y		y			y		y									
18	51	M	3	33	2	y				y	y						y		y						
19	56	M	8	53	3	y			y	y	y	y		y	y		y		y			y		y	
20	63	M	1	24	1		y				y													y	
21	72	M	3	31	2				y	y	y	y						y						y	
22	55	M	2	46	2	y							y	y	y	y									

S.No	Age	Sex	Duration of Disease	UPDRS Score	Hoehn & Yahr stage	NON-MOTOR SYMPTOMS																		
						Drooling	Taste / Smell	Swallow	Constipation	Urgency	Nocturia	Dizziness	Pains	Dreams	Insomnia	Sleepiness	Memory	Anxiety	Depression	Hallucination	Sexual dysfunction	Falls	RLS	Sweating	Weight Loss
23	59	M	2	42	2		y				y				y	y			y					
24	52	M	1	33	1				y										y					
25	55	M	1.5	27	1		y					y	y											
26	60	F	3	27	1						y				y				y					
27	67	M	5	49	2	y		y	y														y	
28	55	M	3	48	2				y	y	y				y								y	
29	61	M	5	55	3	y			y	y	y	y		y			y			y		y			
30	66	M	3	31	2	y			y		y													
31	58	M	1	26	1		y		y				y											
32	68	M	5	36	3	y	y			y	y		y	y	y	y						y	y	
33	60	M	6	45	3			y	y	y	y	y		y			y			y		y	y	
34	73	M	3	52	3	y	y	y	y	y	y	y					y		y		y		y	y
35	72	M	1	32	2				y		y	y							y					
36	78	F	2	37	2	y				y	y						y							
37	55	F	1	29	1		y						y											
38	62	M	1.5	32	1		y										y		y					
39	78	M	1.5	63	2				y		y								y				y	y
40	60	M	1	22	1		y		y				y											
41	55	M	3	43	2.5	y		y	y			y					y							
42	62	M	2	42	2	y			y			y		y										
43	68	M	15	68	3	y	y	y	y	y					y		y		y	y		y		y
44	62	M	9	50	2.5	y	y		y					y					y					y
45	56	F	2	36	1.5		y			y					y				y		y			
46	60	M	4	60	2		y		y	y	y	y	y						y				y	y
47	70	M	3	79	3	y	y		y	y	y		y	y			y		y	y		y		

S.No	Age	Sex	Duration of Disease	UPDRS Score	Hoehn & Yahr stage	NON-MOTOR SYMPTOMS																			
						Drooling	Taste / Smell	Swallow	Constipation	Urgency	Nocturia	Dizziness	Pains	Dreams	Insomnia	Sleepiness	Memory	Anxiety	Depression	Hallucination	Sexual dysfunction	Falls	RLS	Sweating	Weight Loss
48	77	M	8	81	3	y		y	y	y	y		y	y		y				y		y		y	y
49	58	M	4	61	2.5	y		y		y	y		y	y										y	
50	62	M	8	61	3	y				y	y		y		y	y	y		y		y			y	
51	60	M	7	48	2				y		y	y					y		y					y	y
52	58	M	2	32	1		y		y			y					y							y	
53	68	M	3	33	2	y					y	y		y											
54	52	M	1	34	1						y	y	y	y					y						
55	62	M	2	32	1			y	y	y	y				y										y
56	57	M	5	70	3	y			y	y	y			y	y		y	y	y			y	y	y	
57	70	M	1	54	2						y	y				y		y							
58	54	M	1.5	34	1					y	y			y											
59	55	M	1	51	2				y	y	y		y								y				
60	65	M	15	67	2.5	y			y						y	y			y					y	
61	65	F	13	109	4	y		y				y	y	y	y		y	y	y			y		y	
62	52	F	2	59	2			y			y		y	y	y									y	
63	69	M	10	78	3	y		y		y	y	y		y						y		y			y
64	58	M	1	24	1		y												y						
65	60	M	2	40	2			y							y	y	y								
66	63	M	1.5	30	1.5						y	y	y		y										
67	70	M	8	89	3	y				y	y						y	y	y			y	y	y	y
68	62	F	5	36	2		y	y					y		y		y								
69	55	M	4	52	2.5				y	y	y									y			y		
70	53	M	2	26	1				y										y		y				
71	60	F	9	80	3	y		y	y	y	y	y			y	y	y					y		y	y
72	70	M	4	38	2					y								y					y	y	y

S.No	Age	Sex	Duration of Disease	UPDRS Score	Hoehn & Yahr stage	NON-MOTOR SYMPTOMS																				
						Drooling	Taste / Smell	Swallow	Constipation	Urgency	Nocturia	Dizziness	Pains	Dreams	Insomnia	Sleepiness	Memory	Anxiety	Depression	Hallucination	Sexual dysfunction	Falls	RLS	Sweating	Weight Loss
73	56	M	3	40	2							y	y						y					y	y
74	58	F	12	122	4	y		y	y		y	y			y	y		y	y			y		y	
75	54	M	1	24	1													y	y		y				
76	66	M	2.5	40	2					y	y			y									y		
77	52	F	1	28	1								y					y							y
78	71	M	6	92	3			y	y	y		y		y		y	y			y		y			
79	55	M	4	64	2.5				y		y				y	y					y				
80	57	F	2	30	1.5		y					y	y												y
81	64	M	2	42	2	y		y										y					y		
82	58	M	5	102	3					y		y		y			y	y		y	y	y		y	y
83	76	M	3	48	2				y						y		y						y		
84	52	F	1	28	1					y			y								y				
85	65	M	0.5	26	1		y																y		
86	59	M	2.5	44	2					y	y				y			y		y					
87	60	M	4	98	3					y	y	y		y			y			y		y		y	y
88	62	M	14	126	4	y		y	y	y	y			y			y					y		y	
89	64	M	1	40	2					y					y				y						
90	67	F	3	48	2.5	y		y				y				y								y	y
91	54	F	1	22	1						y		y					y							y
92	70	F	8	110	3	y			y	y		y			y		y	y		y		y		y	y
93	52	M	2.5	32	2							y						y			y				y
94	55	M	1	24	1		y			y									y						
95	60	M	2	46	2				y	y							y		y				y		
96	56	F	3	50	2.5			y			y				y	y	y							y	
97	58	M	3	48	2						y	y									y		y		y

S.No	Age	Sex	Duration of Disease	UPDRS Score	Hoehn & Yahr stage	NON-MOTOR SYMPTOMS																				
						Drooling	Taste / Smell	Swallow	Constipation	Urgency	Nocturia	Dizziness	Pains	Dreams	Insonmia	Sleepiness	Memory	Anxiety	Depression	Hallucination	Sexual dysfunction	Falls	RLS	Sweating	Weight Loss
98	53	M	1.5	30	1		y						y					y							
99	57	F	2	36	1.5							y	y		y	y										y
100	64	M	12	106	4				y	y	y			y	y	y	y	y	y			y	y			

Y – yes

MASTER CHART

S.No	Age	Sex	Duration of Disease	UPDRS Score	Hoehn & Yahr stage	NON-MOTOR SYMPTOMS																			
						Drooling	Taste / Smell	Swallow	Constipation	Urgency	Nocturia	Dizziness	Pains	Dreams	Insonmia	Sleepiness	Memory	Anxiety	Depression	Hallucination	Sexual dysfunction	Falls	RLS	Sweating	Weight Loss
1	56	M	5	49	3	Y				y	y	y		y	y	y	y		y	*y*		y		y	
2	66	M	2	30	1.5		y		y				y		y										
3	59	M	1	27	1		y				y								y						
4	65	M	2	23	2	y			y	y	y													y	
5	69	F	4	42	1.5				y	y	y	y													y
6	60	F	9	52	3	y		y	y	y				y		y	y		y			y		y	
7	62	M	4	41	2		y			y	y		y					y			y				
8	60	M	2	25	1.5								y				y		y						
9	53	M	2	52	3	y	y		y	y	y		y	y						y		y		y	
10	64	F	6	54	3	y		y	y	y	y	y			y	y		y				y			
11	54	M	2	29	1		y				y								y						
12	51	F	2	30	1				y	y	y														
13	65	M	4	44	2	y			y		y		y					y							
14	50	F	7	49	3	y		y	y		y	y					y			y	y	y		y	y
15	52	F	4	52	2				y		y				y				y					y	
16	46	M	2	51	3	y	y	y	y	y	y	y					y		y			y		y	
17	52	F	8	44	2				y		y			y		y									
18	51	M	3	33	2	y				y	y						y		y						
19	56	M	8	53	3	y			y	y	y	y		y	y		y		y			y		y	
20	63	M	1	24	1		y				y													y	
21	72	M	3	31	2				y	y	y	y						y						y	
22	55	M	2	46	2	y							y	y	y	y									

S.No	Age	Sex	Duration of Disease	UPDRS Score	Hoehn & Yahr stage	NON-MOTOR SYMPTOMS																		
						Drooling	Taste / Smell	Swallow	Constipation	Urgency	Nocturia	Dizziness	Pains	Dreams	Insomnia	Sleepiness	Memory	Anxiety	Depression	Hallucination	Sexual dysfunction	Falls	RLS	Sweating	Weight Loss
23	59	M	2	42	2		y				y				y	y			y					
24	52	M	1	33	1				y										y					
25	55	M	1.5	27	1		y					y	y											
26	60	F	3	27	1						y				y				y					
27	67	M	5	49	2	y		y	y														y	
28	55	M	3	48	2				y	y	y				y								y	
29	61	M	5	55	3	y			y	y	y	y		y			y			y		y			
30	66	M	3	31	2	y			y		y													
31	58	M	1	26	1		y		y				y											
32	68	M	5	36	3	y	y			y	y		y	y	y	y						y	y	
33	60	M	6	45	3			y	y	y	y	y		y			y			y		y	y	
34	73	M	3	52	3	y	y	y	y	y	y	y					y		y		y		y	y
35	72	M	1	32	2				y		y	y							y					
36	78	F	2	37	2	y				y	y						y							
37	55	F	1	29	1		y						y											
38	62	M	1.5	32	1		y										y		y					
39	78	M	1.5	63	2				y		y								y				y	y
40	60	M	1	22	1		y		y				y											
41	55	M	3	43	2.5	y		y	y			y					y							
42	62	M	2	42	2	y			y			y		y										
43	68	M	15	68	3	y	y	y	y	y					y		y		y	y		y		y
44	62	M	9	50	2.5	y	y		y					y					y					y
45	56	F	2	36	1.5		y			y					y				y		y			
46	60	M	4	60	2		y		y	y	y	y	y						y				y	y
47	70	M	3	79	3	y	y		y	y	y		y	y			y		y	y		y		

S.No	Age	Sex	Duration of Disease	UPDRS Score	Hoehn & Yahr stage	NON-MOTOR SYMPTOMS																			
						Drooling	Taste / Smell	Swallow	Constipation	Urgency	Nocturia	Dizziness	Pains	Dreams	Insomnia	Sleepiness	Memory	Anxiety	Depression	Hallucination	Sexual dysfunction	Falls	RLS	Sweating	Weight Loss
48	77	M	8	81	3	y		y	y	y	y		y	y		y				y		y		y	y
49	58	M	4	61	2.5	y		y		y	y		y	y										y	
50	62	M	8	61	3	y				y	y		y		y	y	y		y		y			y	
51	60	M	7	48	2				y		y	y					y		y					y	y
52	58	M	2	32	1		y		y			y					y							y	
53	68	M	3	33	2	y					y	y		y											
54	52	M	1	34	1						y	y	y	y					y						
55	62	M	2	32	1			y	y	y	y				y										y
56	57	M	5	70	3	y			y	y	y			y	y		y	y	y			y	y	y	
57	70	M	1	54	2						y	y				y		y							
58	54	M	1.5	34	1					y	y			y											
59	55	M	1	51	2				y	y	y		y								y				
60	65	M	15	67	2.5	y			y						y	y			y					y	
61	65	F	13	109	4	y		y				y	y	y	y		y	y	y			y		y	
62	52	F	2	59	2			y			y		y	y	y									y	
63	69	M	10	78	3	y		y		y	y	y		y						y		y			y
64	58	M	1	24	1		y												y						
65	60	M	2	40	2			y							y	y	y								
66	63	M	1.5	30	1.5						y	y	y		y										
67	70	M	8	89	3	y				y	y						y	y	y			y	y	y	y
68	62	F	5	36	2		y	y					y		y		y								
69	55	M	4	52	2.5				y	y	y									y			y		
70	53	M	2	26	1				y										y		y				
71	60	F	9	80	3	y		y	y	y	y	y			y	y	y					y		y	y
72	70	M	4	38	2					y								y					y	y	y

S.No	Age	Sex	Duration of Disease	UPDRS Score	Hoehn & Yahr stage	NON-MOTOR SYMPTOMS																				
						Drooling	Taste / Smell	Swallow	Constipation	Urgency	Nocturia	Dizziness	Pains	Dreams	Insomnia	Sleepiness	Memory	Anxiety	Depression	Hallucination	Sexual dysfunction	Falls	RLS	Sweating	Weight Loss
73	56	M	3	40	2							y	y						y					y	y
74	58	F	12	122	4	y		y	y		y	y			y	y		y	y			y		y	
75	54	M	1	24	1													y	y		y				
76	66	M	2.5	40	2					y	y			y									y		
77	52	F	1	28	1								y					y							y
78	71	M	6	92	3			y	y	y		y		y		y	y			y		y			
79	55	M	4	64	2.5				y		y				y	y					y				
80	57	F	2	30	1.5		y					y	y												y
81	64	M	2	42	2	y		y										y					y		
82	58	M	5	102	3					y		y		y			y	y		y	y	y		y	y
83	76	M	3	48	2				y						y		y						y		
84	52	F	1	28	1					y			y								y				
85	65	M	0.5	26	1		y																y		
86	59	M	2.5	44	2					y	y				y			y		y					
87	60	M	4	98	3					y	y	y		y			y			y		y		y	y
88	62	M	14	126	4	y		y	y	y	y			y			y					y		y	
89	64	M	1	40	2					y					y				y						
90	67	F	3	48	2.5	y		y				y				y								y	y
91	54	F	1	22	1						y		y					y							y
92	70	F	8	110	3	y			y	y		y			y		y	y		y		y		y	y
93	52	M	2.5	32	2							y						y			y				y
94	55	M	1	24	1		y			y									y						
95	60	M	2	46	2				y	y							y		y				y		
96	56	F	3	50	2.5			y			y				y	y	y							y	
97	58	M	3	48	2						y	y									y		y		y

S.No	Age	Sex	Duration of Disease	UPDRS Score	Hoehn & Yahr stage	NON-MOTOR SYMPTOMS																				
						Drooling	Taste / Smell	Swallow	Constipation	Urgency	Nocturia	Dizziness	Pains	Dreams	Insonmia	Sleepiness	Memory	Anxiety	Depression	Hallucination	Sexual dysfunction	Falls	RLS	Sweating	Weight Loss
98	53	M	1.5	30	1		y						y					y							
99	57	F	2	36	1.5							y	y		y	y										y
100	64	M	12	106	4				y	y	y			y	y	y	y	y	y			y	y			

Y – yes